Primary Amenorrhea

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Introduction

PRIMARY AMENORRHEA, or the absence of any menstrual function, is the normal state for prepubertal girls and does not become a disease or symptom until the expected date of puberty. The secular trend in the date of menarche now places the median age at 13. Of normal girls, 95 percent will have had their first period by age 15; the absence of menstruation beyond that date can be defined as primary amenorrhea, although it may not turn out to herald significant disease. Because breast development ordinarily antedates menarche by approximately two years, the absence of progressive breast enlargement by age 13 can similarly be taken as a stimulus to evaluation, if not as definitive evidence of abnormality.

It should be emphasized that most suspected abnormalities of pubertal development turn out to be variations of the normal, with excellent prognosis, rather than disease. With this probability in mind, a conservative and expectant approach to diagnosis and therapy is usually appropriate, but the clinician should be aware of screening tests that provide either strong reassurance or an early alert to true disease.

Normal Physiology Recapitulated

Dr. Odell has outlined the normal physiology of menstruation. Although the event that triggers puberty is unknown, normal menses ultimately require the presence of normal hypothalamic, pituitary and ovarian function.

Required Functions

The hypothalamus must secrete gonadotropin releasing hormone (GnRH) both at a basal level and, when exposed to high estrogen levels, in an abrupt surge. The pituitary must be able to produce both gonadotropins: FSH initiates follicular development and estrogen synthesis and, when appropriate follicular development has occurred, LH triggers ovulation.

The ovary secretes estrogen in progressively increasing amounts over an approximately 12-day period; when the plasma estradiol reaches a critical level, positive feedback stimulates both an increase in GnRH output and an enhanced pituitary response to GnRH.[30] The result is a sudden surge of both FSH and LH, leading to ovulation. Following ovulation, the corpus luteum secretes large amounts of progesterone. Finally, if pregnancy does not occur, both estrogen and progesterone levels fall, and several days later menstrual flow begins.

The uterus must be able to respond to both hormones, and, finally, there must be a patent cervix and introitus in order for the menstrual blood to be shed.

Absence of an Excess of Three Classes of Hormones

Three types of hormones, when secreted in excess, are capable of interfering with an otherwise intact hypothalamic-pituitary-ovarian-uterine system. The three potentially interfering hormones are cortisol, prolactin and androgens. The evaluation of patients with delayed menarche must thus be addressed both to the *presence* of hypothalamic, pituitary and ovarian competence and to the *absence* of those hormones capable of intruding on the system.

Central Causes of Primary Amenorrhea

Central causes of primary amenorrhea refer to hypothalamic and pituitary disorders that cause either absence of the releasing hormone or failure of the pituitary gland to respond to it.[31] The clinical manifestations of these defects are due to absence of both gonadotropins, with resultant deficiency in both breast development and menstrual function.

Absence of Hypothalamic Releasing Hormone

- *Physiologically delayed puberty*

The onset of puberty appears to be genetically determined. Therefore, particularly in a child who is growing slowly, the story that the mother or sisters had a later onset of puberty is strong reassurance that the patient will ultimately develop periods of her own. Nevertheless, when a child of 14 or 15 has not yet undergone breast development, a plasma FSH determination should be obtained. Since concentrations of FSH (and LH) fluctuate rhythmically each 10 to 20 minutes, the average of three specimens is more precise than a single determination. A low or normal value is consistent with later normal development. If

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the FSH is elevated, it provides evidence of ovarian failure and should stimulate a further workup.

- *Nutritional causation*

There is considerable evidence that the onset of puberty is tied to the attainment of a critical body weight.[32] Children who are short and growing slowly but steadily often have a late menarche. Children who are pathologically short, particularly when they have been nutritionally deprived because of emotional factors, often have a late puberty. In addition, disorders such as regional enteritis are often clinically subtle in teenage girls and may also cause amenorrhea. In the presence or normal or low LH and FSH levels and primary amenorrhea, this category of causes should be carefully considered. Professional athletes or marathon runners also have a high incidence of amenorrhea probably related to alterations in body fat:muscle ratios, factors which may be implicated in this nutritional category.

- *Deficiency of gonadotropin releasing hormone*

Although more common in males, idiopathic absence of GnRH occurs in females as well. It is occasionally associated with absence (anosmia) or impairment (hyposmia) of the ability to smell. When either of these defects is found in association with pubertal delay, the diagnosis of the Kallman syndrome is established. The serum gonadotropin will be found to be low, and replacement therapy is appropriate.

In a patient with a normal sense of smell, it is extraordinarily difficult to make the differential diagnosis between idiopathic gonadotropin releasing hormone deficiency and physiological delay of puberty. In a normal prepubertal girl, GnRH administration increases FSH in relation to LH to a much greater extent then following puberty or in most patients with GnRH deficiency. Consequently, this GnRH test may help to distinguish GnRH deficiency from delayed puberty. In addition, the administration of GnRH ought to distinguish patients who lack GnRH from those with pituitary disease who are simply unable to respond to GnRH; unfortunately, many reports have documented an overlap in results of such tests.[33] In other patients, however, daily administration of GnRH awakens a gonadotropin response by the pituitary that is initially sluggish. There is thus considerable ambiguity in results. Recent studies from various laboratories have suggested that the hypothalamic defect is more complex than was originally supposed and that various abnormalities of other releasing hormones and tropic hormone responses may be involved. Suprasellar tumors (such as craniopharyngiomas, teratomas) may also produce GnRH deficiency and amenorrhea.

Pituitary Deficiency

The inability to synthesize gonadotropin despite adequate GnRH stimulation would, of course, also be a cause of primary amenorrhea. As an isolated biosynthetic defect, this failure appears to be less common than GnRH deficiency. As a component of hypopituitarism, however, gonadotropin deficiency occurs early and, therefore, children with developing pituitary insufficiency may have a defect in gonadotropin production, while thyroid and adrenal function remain normal. Ordinarily, however, growth hormone is impaired approximately as early as is gonadotropin; therefore, children who have primary amenorrhea because of pituitary deficiency usually show a defect in growth. It is exactly in this context that plotting a child's growth pattern is the most valuable (and simultaneously the cheapest) laboratory test available. If the child maintains a growth pattern consistent with the rate of growth shown in earlier years, strong reassurance against acquired pituitary growth hormone deficiency can be inferred.

The pituitary lesions that may be responsible for gonadotropin deficiency include tumor, granuloma and infarction. All are relatively uncommon, of course, but the commonest one, pituitary tumor, can often be shown by tomograms of the sella; one is looking in particular for asymmetric contours of a normal-size sella or enlargement of the sella. Suprasellar calcification may indicate the presence of a craniopharyngioma which can cause GnRH deficiency or directly involve the pituitary (or both). Measurement of the serum prolactin will also alert the physician to the approximately 30 percent to 50 percent of pituitary tumors that were formerly thought to be without function but are known to be prolactin-secreting.

Physical examination also helps in the elucidation of gonadotropin deficiency. In a child who was formerly normal, had breast development on time but then failed to menstruate because of pituitary deficiency secondary to a tumor, a growth defect may be shown at approximately the time of expected menstruation. In contrast, in a child who is short and unable to secrete estrogen be-

cause of an ovarian defect, growth impairment would have been shown much earlier.

It cannot be emphasized too often that plasma or serum gonadotropin measurements are the best way to establish the site of the abnormality. If the gonadotropin levels are low or normal, a central defect can be presumed; if an x-ray study of the skull shows no abnormalities, one can wait, although temporary estrogen therapy can be considered for psychological reasons. If the gonadotropin values are high, the defect is in the ovary.

Ovarian Defects

Ovarian inability to produce estrogen and progesterone despite adequate gonadotropin stimulation is a well-established source of primary amenorrhea. Three principal classes of defect can be delineated: chromosomal errors in gonadal differentiation, primary biosynthetic defects in estrogen manufacture and excess androgen production.

Defective Ovarian Differentiation

The classic ovarian defect is the Turner syndrome, or ovarian agenesis.[34] In the complete syndrome, a 45,X karyotype is associated with a variety of congenital anomalies, growth retardation evident by about the third or fourth year of life, and complete lack of estrogen. These patients are usually promptly recognized on physical examination, and the suspected diagnosis can be confirmed by a chromatin-negative buccal smear and elevated plasma FSH.

The variants of gonadal dysgenesis provide somewhat greater difficulty with diagnosis and, therefore, are worth individual mention.[35]

- *Mosaic gonadal dysgenesis*

These patients have a mixture of abnormal and normal cells (45,X/46,XY). For reasons that are intuitively likely but not yet quantitatively understood, these patients have partial manifestation of the Turner syndrome; any combination of anomalies, short stature and menstrual difficulty may be seen. If the anomalies are trivial and the growth defect minimal, primary amenorrhea of this origin can be difficult to recognize, but the elevation of the FSH should provide an alert.

- *Pure gonadal dysgenesis*

Occasional patients with either a 46,XY or a 46,XX karyotype have the same gonadal defect as patients with the Turner syndrome but have neither the anomalies nor the growth retardation. In the absence of short stature in a patient, a clinician may have difficulty recognizing the diagnosis. Clues are the absence of breast development and a normal but small uterus. In those who are 46,XY there will be a chromatin-negative buccal smear, and in both groups of patients gonadotropin will be elevated.

- *Mixed (or asymmetric) gonadal dysgenesis*

In mixed gonadal dysgenesis, the patient has a streak gonad plus a testis. Most patients come to attention as newborns because of ambiguity of the external genitalia. If the ambiguity is overlooked, they are usually recognized in early puberty because of virilization. But they may escape diagnosis until absence of breast development and primary amenorrhea are recognized. The karyotypic defect varies, but most often it is a mosaic pattern, that is 45,X/46,XY. The characteristic laboratory findings are a chromatin-negative buccal smear, an elevated plasma testosterone and high gonadotropin.

Difficulty With Estrogen Biosynthesis

Several defects in steroid biosynthesis may result in a decreased synthesis of estrogens. These include:

- *The 17-hydroxylase deficiency*

A deficiency of the 17-hydroxylase enzyme in the ovaries and adrenals produces a decrease in both estrogen and cortisol synthesis. These patients lack estrogen effects, are usually hypertensive, have low blood cortisol, and elevated progesterone and corticosterone concentrations.

- *The 17-ketosteroid reductase deficiency*

The 17-ketosteroid reductase deficiency results in an inability or decreased ability to convert androstenedione to testosterone and estrone to estradiol. In an XY male, this results in a phenotypic female with absent uterus, amenorrhea and hirsutism. The low testosterone concentrations *in utero* result in pseudohermaphroditism, but the elevated androstenedione produces hirsutism.

- *Defects in early steps of steroidogenesis*

Deficiencies of the cholesterol desmolase or 3βol dehydrogenase enzymes usually produce death early in infancy unless diagnosed and treated. They have not yet been reported to

present in later life as amenorrhea, but this would be anticipated since sex steroid production would be deficient.

Excess Androgen Production

Excess androgen production as a cause of primary amenorrhea is seen primarily with variants of the Stein-Leventhal or polycystic ovary syndrome (PCO). Although usually noted for secondary amenorrhea, the PCO syndrome can cause primary amenorrhea. Patients have breast development, usually have some degree of hirsutism and may be quite muscular. FSH is normal, but LH is usually high normal, though acyclic. Endocrine findings are extremely variable in these patients, but there is usually some elevation of plasma androgens and estrone.

Absence of Uterus

Absence of the uterus, with intact female endocrine function, produces a unique history and physical examination findings that result in the diagnosis of the Rokitansky syndrome. At birth, the patient has a normal newborn appearance, although in some cases the vagina is also absent. Growth and development, with timely breast enlargement, normal pubic hair, and normal estrogen production and serum FSH contribute to the picture of a normal puberty. Yet, for no known reason, the uterus is missing. On examination the patient is shown to have a normal XX karyotype, and an ultrasound examination of the pelvic organs or laparoscopy may be needed to confirm the absence of the uterus.

Absence of the uterus may be associated with a radically different disorder: male pseudohermaphroditism. The classic example is testicular feminization or androgen resistance syndromes. In these, the patients are genetic males who lack the cell receptor for testosterone. They have plasma testosterone concentrations which are normal for a male, but are biochemically unable to respond to this testosterone. In the fetus the testes secrete müllerian-duct inhibiting hormone and thus suppression of müllerian structures occurs. Therefore, these patients have no uterus and a shallow blind vagina; lacking effective testosterone, however, they do not differentiate male internal or external genitalia. They often come to pediatric attention because of an inguinal hernia caused by

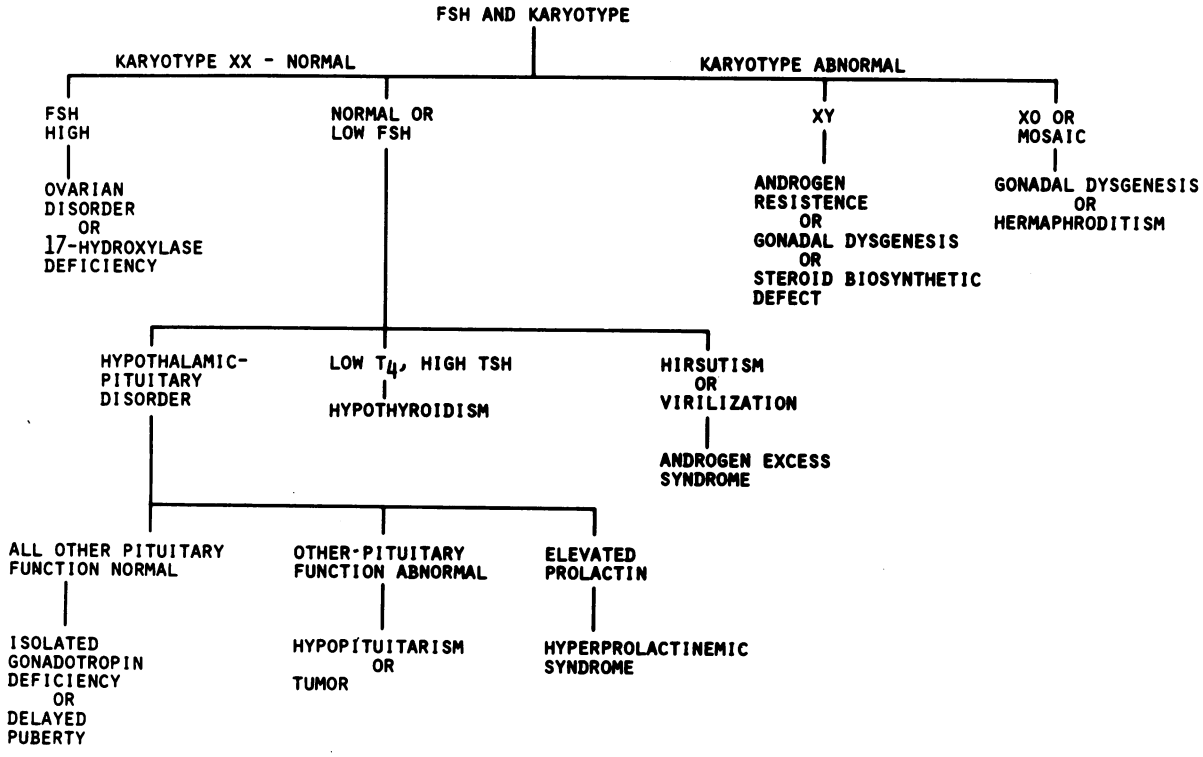

Figure 25.—Outline for the diagnosis of patients with primary amenorrhea.

the attempted descent of the testis. Otherwise, they develop in a normal female pattern, having the breast development of normal female puberty, but lacking a uterus they cannot have periods. The findings on physical examination in complete androgen resistance are a critical clue to this diagnosis: the patient is normal in height, has breast development, but has neither pubic or axillary hair nor a palpable uterus. The laboratory findings show elevated plasma testosterone (for a female) and estradiol but only minimally elevated FSH. The critical laboratory finding is an XY normal male karyotype.

Milder variants of this disease with partial androgen resistance accompanied by some degree of genital ambiguity or pubertal virilization, are also seen. Paradoxically, although milder, they are less difficult to diagnose because the virilization in a patient with primary amenorrhea suggests the diagnosis. The 17 ketosteroid reductase enzyme deficiency previously mentioned has often been mistaken for incomplete androgen resistance.

Interfering Hormones

Three types of hormones may interfere with the onset of normal menstrual function. Cortisol in the context of adrenal hyperfunction and the Cushing syndrome is well known. Although the clinical manifestations may not be striking, other features of cortisol excess will usually be evident on physical examination. In other words, primary amenorrhea is not likely to be the only feature of the Cushing syndrome. For confirmation, the usual tests for the Cushing syndrome should be undertaken; in the simplest screening test, 1 mg of dexamethasone is given at midnight and a plasma cortisol determination is done the following morning. Cortisol values less than 5 μg per dl eliminate the Cushing syndrome from consideration.

Prolactin elevation may be a cause of primary amenorrhea. Although much more common as a cause of secondary amenorrhea, prolactin elevation has also been reported with pituitary tumors as a cause of primary amenorrhea.

Finally, androgen excess can also prevent the onset of normal menstrual function. Adrenal androgens may be hypersecreted either by adrenal tumors, which can develop at any time, or in the syndrome of congenital adrenal hyperplasia. Most patients with congenital adrenal hyperplasia come to attention as newborns because of genital ambiguity. Very occasionally, the onset of the defect is manifest at puberty; such patients have absent or minimal breast development, excessive hair growth and primary amenorrhea. They are chromatin-positive, and their androgen levels are high.

Workup and Evaluation

The workup appropriate to investigate primary amenorrhea has been implied in the preceding sections. Although many laboratory tests can be helpful, the history and physical examination should provide the clue to the diagnosis most of the time, making one or two confirmatory laboratory tests adequate.

The history should emphasize the family pattern of menstrual onset, previous growth and development, recent changes in general health and the onset of breast development. Physical examination should focus on height, degree of muscularity, the anomalies of the Turner syndrome, hirsutism or other signs of virilization, presence or absence of breast enlargement, and presence or absence of a uterus.

If there is no evidence of estrogen secretion, plasma FSH should be quantified to orient the diagnosis toward a central or ovarian cause. A karyotype is indicated if the gonadotropin value is high or if there is no uterus palpable. Based on the FSH and karyotype results the patients may be placed into one of the diagnostic categories outlined in Figure 25. Measurements of other pituitary hormones, thyroid hormones, androgens or steroid hormone precursors should then be made if indicated.

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